

REMARKS/ARGUMENTS

Claims 1-11 and 23-28 were examined on the merit in the final Office action mailed June 19, 2008. Claims 1-11 and 23-28 have been amended. Support for the amendment can be found in the present application. Accordingly, no question of new matter should arise, and entry of this amendment is respectfully requested.

Claims 1-36 are pending in the application. Claims 12-22 and 29-36 have been previously withdrawn from consideration by the examiner as drawn to the non-elected invention. Applicants specifically reserve the right to file one or more divisional applications to the non-elected subject matter.

By the above amendment, Applicants have amended Claims 1-11 and 23-28 to more particularly and distinctly define the invention so as to overcome the technical rejection and to define the invention patentably over the prior art.

The applicants submit the following remarks to address the Examiner's rejection which taken in combination with the amendments presented herewith attempt to address each of the Examiner's concerns.

I. Rejection under 35 USC 103(a):

The Examiner has rejected Claims 1-11 and 23-28 under 35 U.S.C 103 (a) as being unpatentable over the disclosures of Markussen et al. (USPN US4,916,212 hereafter '212) in view of Schweden et al. (USPN 5,672,487 hereafter '487), as evidenced by Hollenberg et al., (Curr Opin Biotechnol.1997 Oct;8(5):554-60,Abstract Only), and Weidemann et al., (FEBS Lett.1989. Oct 23;257(1):31-4) for the reasons of record and the reasons set forth herein.

It appears to be that there was a typo in the Office Action mailed on June 19,

2009, where the US patent number for US4,962,212 should have been US4,916,212 (Office Action, p. 3 of 7, Paragraph 2).

Claims 1 -11 and 23-28 have been rejected under 35 U.S.C. § 103(a) over Markussen et al. (USPN US4,916,212 hereafter '212) in view of Schweden et al. (USPN 5,672,487 hereafter '487), as evidenced by Hollenberg et al., (Curr Opin Biotechnol.1997 Oct;8(5):554-60,Abstract Only), and Weidemann et al., (FEBS Lett.1989. Oct 23;257(1):31-4)

The Examiner states that the instant invention is a composition comprising a yeast promoter followed by a signal peptide from either *Schwanniomyces occidentalis* glucoamylase signal peptide sequence or *Carcinus maenas* crustacean hyperglycemic hormone signal peptide sequence followed by an insulin pre-pro-peptide. According to the Examiner, the Markussen teaches a DNA construct comprising insulin precursor expressed in yeast meeting the limitation of instant claims 1, 4-11, 23 and 25.

The Markussen does not teach a DNA construct with the signal peptide sequence from *Schwanniomyces occidentalis* or *Carcinus maenas* crustacean hyperglycemic hormone. The Schweden teaches construction vector for the expression of recombinant proteins from the yeast *Hansenula polymorpha* including yeasts with the glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* and the leader sequence from hyperglycaemic hormone of the shore crab (*Carcinus maenas*).

Applicants would like to draw Examiner's attention to the fact that the **only** disclosure of glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* is in a citation for a reference in the background section wherein the glucoamylase leader sequence was not a part of the DNA constructs taught by Schweden: See col. 1, lines 28-36. There is no other disclosure of glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* in Schweden.

“In the yeast *Hansenula polymorpha*, the glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* is recognized as signal sequence, and it is possible to secrete correctly processed glucoamylase (G. Gellissen et al., *Biotechnology* 9 (1991) 291-295). However, **this signal sequence does not lead to the secretion of gene products foreign to yeasts**, for example it is not possible to secrete the protein hirudin therewith.”

Thus, as evident from the above disclosure of Schweden, the glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* is a recognized signal sequence in yeast *Hansenula*; it does not lead to the secretion of a gene product foreign to yeast i.e. heterologous protein. Insulin used in this invention is also a heterologous protein. Thus, based on the teaching of Schweden, signal peptide sequence is not suitable for the production of insulin in yeast. Under the proper legal standard, a reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). As evident from the above mentioned teaching of Schweden, the prior art teaches away from the use of glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* for secretion of insulin. When the prior art teaches away from the claimed solution as presented here, obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition.

One cannot use hindsight reconstitution to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. (*In re Fine*, 837 F. 2d 1071, 1075, 5 USPQ2d, 1596, 1600, Fed. Circ. 1988).

The Examiner further states that the Schweden provides a rationale and

motivation to use a construct comprising vectors for the use of large (i.e. commercial scale) secretory expression of recombinant proteins in *Hansenula polymorpha* yeasts using signal sequences from *Schwanniomyces occidentalis* or the signal sequences of the crustacean hyperglycemic hormone from *Carcinus maenas*. Further, the Examiner states that Schweden teaches that the use of these signal sequences in this yeast is known, tested, proven, successful and predictable. Moreover, the Schweden teaches that any generic protein may be used in the yeast expression system, "in particular proteins which are foreign to yeast i.e. heterologous, in the yeast *Hansenula*, which ensures **efficient secretion** and correct processing for a large number of proteins" See col. 1, lines 36-41 (Office Action, page 5, paragraph 1). The above saying is a mere statement which is not supported by the any underpinning facts. The Examiner's statement that the use of these signal sequence is proven, successful and predictable does not find any support in the Schweden. The statement concerning efficient secretion is ambiguous as it is not supported by experimental evidence. This asserted statement in the prior art was broad and general without sufficient direction to practice the claimed invention. Moreover, the asserted prior art provided no working examples of the invention claimed in this patent application.

In Schweden, example 1 only exemplifies the use of a leader sequence from shore crab (Seq. ID No. 1) for the construction of vector for the secretory expression of hirudin in yeast *Hansenula polymorpha*. Example 2 relates to transformation of said expression vector. Example 3 relates to isolation of stable clones and Example 4 & Example 5 relates to expression and fermentation of recombinant yeast strain encoding hirudin gene respectively. At the end of fermentation, Schweden clearly states that the recombinant yeast fermented in this way provided a gene product (hirudin) which is 100% correctly processed. See col. 6, lines 30-32. The yield of hirudin obtained by using this process is not provided anywhere in the Schweden.

In Schweden, the only leader sequence used in the process is the leader sequence from shore crab (Seq. ID No. 1). There is no disclosure or enablement for the use of

leader sequence from *Schwanniomyces occidentalis*. There is no disclosure of insulin in the Sweden. No other protein other than hirudin is specifically disclosed in the Sweden. Further, the process enabled only for the production of recombinant hirudin. No other recombinant protein is enabled. The process cannot be extrapolated to cover all the recombinant proteins. There are large number of recombinant protein products available in the market, for example insulin aspart, insulin lispro, insulin glargine, insulin glulisine, insulin detemir, human choriogonadotropin, Follicle-stimulating hormone, Luteinizing hormone, Somatotrophin, Erythropoietin alpha, Erythropoietin beta, Erythropoietin omega, Darbepoetin, Filgrastim, Surgramostim, Human blood coagulation factors Factor VIII, Factor IX, Factor VII A, Thrombolytic agents, Alteplase, Tenecteplase, Saruplase, Lepirudin, Desirudin, Human interferons Interferon alpha-2b, Interferon beta-1b, Interferon gamma, Interleukin-2, Interleukin-11, Dorsase alpha, Glucocerebrosidase, etc. These recombinant proteins vary structurally and functionally from each other. The process, which is useful for making one recombinant protein, may not be useful for manufacturing the other recombinant protein even when they belong to the same class. For example, the process, which results in high yield of regular human insulin, is not useful for the production of insulin glargine. Moreover, hirudin and insulin are structurally and functionally class apart recombinant products. Some of the differences between the two are highlighted below in Table 1.

Table 1:

	Hirudin	Insulin
Amino acid	65 amino acids	51 amino acids
Function	Anticoagulant	Antihyperglycemic
Mechanism of Action	Hirudin is a potent thrombin-specific protease inhibitor. It forms a stable non-covalent complex with alpha-thrombin, thereby abolishing its ability to cleave fibrinogen.	Insulin binds to insulin receptor and generates a cascade of phosphorylation reactions. It decreases the blood glucose level. Insulin facilitates entry of glucose into muscle, adipose and several other tissues by acting on GluT4 transporter.
Origin	Salivary glands of medicinal leeches	Pancreas of mammals
No. of chain	Single chain molecule	Two chain – A and B chains
Class	Protease inhibitor I14 (hirudin) family	Hormone

Molecular Weight	6986 Da	5808 Da
Disulphide bonds	6-14,16-28,22-39	A6-A11; A7-B7; A20-B19
Inter-chain disulphide bond	No	01
Amino acid sequence	ITYTDCTESGQNL CLCEGSNVCCKGN KCILGSNGEENQC VTGEGTPKPKQSHN DGDFFEEIPEEYLQ	GIVEQCCTSI CSLYQLENYC N – A chain FVNQHLCGSHLVEALYLVC GERGFFYTPKT - B chain

One test is not sufficient where there was no adequate basis for concluding the other claimed compounds would behave the same way (In re Lindner, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972)).

One of skill in the art could envisage the use of the process involving leader sequence obtained from shore crab as claimed in Schweden for the production of hirudin analogs, hirudin derivative and for hirudin like molecule. Schweden, however, does not describe or suggest the use of the leader sequence obtained from shore crab for the high expression of insulin precursor. Further, the use of such a process for the production of insulin will require undue experimentation.

The enablement requirement is satisfied when one of skill in the art after reading the specification, could practice the claimed invention without undue experimentation (AK Steel Corp. V. Sollac, 344 F.3d, 1234, 1244, 68 USPQ2d 1280 (Fed. Circ. 2003)). The Schweden only discloses the use of the leader sequence obtained from shore crab for the production of correctly processed hirudin. The Markussen patent teaches the use of MF-alpha leader sequence for the production of pre-pro-insulin. There is no teaching, suggestion or motivation in the Markussen to replace the MF-alpha leader sequence for leader sequence obtained from shore crab (*Carcinus maenas*). MF-alpha leader sequences differ widely from the *Carcinus maenas* crustacean hyperglycemic hormone signal peptide sequences in terms of their origin as well as sequence. Thus, it would not be obvious to a person of ordinary skill in the art to combine the teachings of Markussen and the Schweden in the manner purported by the examiner. For these reasons claim 1

and dependent claims 2-11, 23, 24 and 28 are allowable over Markussen in view of Schweden.

Decomposing an invention into its constituent elements, finding each element in the prior art and then claiming it is easy to reassemble these elements into the invention, is a forbidden ex port analysis. (In re Mahurkar Patent Litigation, 831 F. Suppl. 1354, 28 USPQ2d 1801 (N.D. III 1993), aff'd, 71 F. 3d 1573, 37 USPQ2d 1138, Fed. Circ.1995).

Additionally, the present applicants have found that the use of the signal peptide sequences from either *Schwanniomyces occidentalis* or *Carcinus maenas* results in unexpected high yield of insulin precursor (Example 4, Table 1).

"[t]hat the prior art taught away from the claimed invention...or (2) that there are new and unexpected results relative to the prior art." Iron Grip Barbell Co., Inc. v. USA Sports, Inc., 392 F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004))."

Further applicants disagree with Examiner that Schweden provided the level of predictability. The Examiner quotes that the use of secretory expression of recombinant proteins in *Hansenula polymorpha* using signal sequences from *Schwanniomyces occidentalis* or *Carcinus maenas* is old and well known in the art and would have been predictable to one of ordinary skill in the art at the time of instant invention. The addition of the insulin pre-pro-peptide was merely a commercial driven choice.

Applicant respectfully would like to draw the examiner's attention to the fact that the use of signal sequences from *Schwanniomyces occidentalis* or *Carcinus maenas* was known only for the production of proteins which were present in the yeast i.e., homologous proteins and for the production of correctly processed heterologous protein. There was no disclosure wherein these signal sequences result in high expression (high yield) of any recombinant protein. Schweden merely made a conclusory statement that the process leads to a high yield of mature proteins, which is not supported by any evidence. See col. 3, lines 11-16.

It is well settled that unexpected results must be established by factual evidence. Mere arguments or conclusory statements...do not suffice (In re De Blauwe, 736, F. 2d.

699, 705, Fed. Circ. 1984).

Further at the time of invention, the recombinant insulin was a well-established product in the market. There were number of patents disclosing specifically the process of producing the insulin using recombinant technology. It would not be envisaged by a person of ordinary skill in the art to predict the high yield of insulin by merely using the signal sequences and process claimed in Schweden especially when there is no disclosure of insulin in the Schweden. As such, claim 1 and dependent claims 2-11, 23, 24 and 28 are allowable over Markussen in view of Schweden.

Claim 25 is directed to a process for the expression of insulin in yeasts, the process includes transforming the yeast with a plasmid that carries the DNA construct of claim 1, culturing the transformed yeasts in an appropriate culture and isolating the insulin containing polypeptide from the culture medium. Claim 25 requires the DNA construct of claim 1. Because claim 25 includes the DNA construct of claim 1, claim 25 and dependent claims 26 and 27 are allowable over Markussen in view of Schweden for the same reasons that claim 1 is allowable over Markussen and Schweden.

As noted above, Markussen teaches a DNA construct comprising insulin precursor expressed in yeast. The Markussen teaches the use of MF-alpha leader sequence for the production of pre-pro-insulin. The Markussen does not teach a DNA construct with the signal peptide sequences from *Schwanniomyces occidentalis* or *Carcinus maenas* crustacean hyperglycemic hormone.

Schweden teaches construction vector for the expression of recombinant proteins from the yeast *Hansenula polymorpha* using the leader sequence from hyperglycaemic hormone of the shore crab (*Carcinus maenas*). The Schweden does not teach the use of leader sequence from *Carcinus maenas* for the production of insulin in high yield.

Hollenberg et al. (Hollenberg CP, Gellissen G. Production of recombinant proteins by methylotrophic yeasts. Curr Opin Biotechnol 1997; 8:554-60) is a general disclosure. Hollenberg discloses the use of methylotrophic yeasts *Hansenula*

polymorpha, *Pichia pastoris* and *Candida boidinii* for the production of recombinant proteins. It does not disclose the use of signal peptide sequence obtained from *Schwanniomyces occidentalis* or *Carcinus maenas*. Hollenberg's general disclosure, however, does not describe or suggest using the DNA construct comprising the above signal sequences for the production of insulin precursor in high yield. Further, even if there was a suggestion to use the DNA construct for the production of insulin, Hollenberg does not enable such a process.

Weidemann et al. (Weidemann et al., FEBS Lett. 1989. Oct23; 257(1):31-4) discloses the cDNA sequence for cloning the precursor of a crustacean hyperglycemic hormone. The cDNA sequence is N-terminally flanked by a Lys-Arg cleavage and C-terminally by the tetrapeptide Gly-Arg-Lys-Lys. Weidemann does not disclose the use of this cDNA sequence for the production of insulin precursor. Further, it does not disclose the cDNA sequence which is not flanked by a cleavage site.

Thus, it would not be obvious to one of ordinary skill in the art to combine the aforementioned arts in the manner purported by the Examiner. For these reasons, independent claim 1 and dependent claims 2-11, 23, 24 and 28 are allowable over Markussen in view of Schweden, Hollenberg and Weidemann.

Claim 25 is directed to a process for the expression of insulin in yeasts, the process includes transforming the yeast with a plasmid that carries the DNA construct of claim 1, culturing the transformed yeasts in an appropriate culture and isolating the insulin containing polypeptide from the culture medium. Claim 25 requires the DNA construct of claim 1. Because claim 25 includes the DNA construct of claim 1, claim 25 and dependent claims 26 and 27 are allowable over Markussen in view of Schweden, Hollenberg and Weidemann for the same reasons that claim 1 is allowable over Markussen in view of Schweden Hollenberg and Weidemann.

Thus, the invention as claimed in our application is a significant technological advancement over the cited prior art. The mere fact that the prior art may be modified in

the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification. The references cited by the Examiner in the latest Office Action failed alone or in combination to suggest any motivation, suggestion, or teaching to come up with an invention as claimed in this patent application.

Here the Examiner relied upon the hindsight to arrive at the determination of obviousness. It is impermissible to use the claimed invention as an instruction manual or “template” to piece together the teachings of the prior art so that the claimed invention is rendered obvious. One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fritch*, 972 F.2d 1260, 23 USPQ 2d at 1783-84 (quoting *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ 2d 1596, 1600 (Fed. Cir. 1988)). *Fritch* thus teaches that the Examiner cannot simply cite different features of the claimed invention from different prior art sources without explaining the motivation to combine or modify the prior art references.

The Supreme Court’s decision in *KSR International. Co. v. Teleflex, Inc., et al.*, 550 U.S.(2007) requires that an Examiner provide “some articulated reasoning with some rationale underpinning to support the legal conclusion of obviousness.” (KSR Opinion at p. 14). An Examiner must “identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does,” (KSR Opinion at p. 15). And, the Examiner must make “explicit” this rationale of “the apparent reason to combine the known elements in the fashion claimed,” including a detailed explanation of “the effects of demands known to the design community or present in the marketplace” and “the background knowledge possessed by a person having ordinary skill in the art.” (KSR Opinion at p. 14). Anything less than such an explicit analysis may not be sufficient to support a *prima facie* case of obviousness. In January 2008 BPAI decision entitled *In re Wada and Murphy* reversed a § 103 rejection because the Examiner did not explain where or how cited art taught or suggested all of the features of a claimed invention.

As noted above that the Office Action fails to specifically address even the expressly recited features of the pending independent and dependent claims. Under the Office's policy of compact prosecution, each claim should be reviewed for compliance with every statutory requirement for patentability in the initial review of the application. (MPEP §707.07(g)). It is submitted that the present application is not sufficiently informal, does not present an undue multiplicity of claims, or exhibit a misjoinder of inventions, so as to reasonably preclude a complete action on the merits. Thus, it is submitted that the Office's failure constitutes a failure to expeditiously provide the information necessary to resolve issues related to patentability that prevents the Applicant from, for example, presenting appropriate patentability arguments and/or rebuttal evidence. (See The Official Gazette Notice of November 7, 2003). Additionally, it is submitted that the Office's failure needlessly encourages piecemeal prosecution, which is to be avoided as much as possible. (MPEP §707.07(g)). Accordingly, in the event that the Office maintains the rejection of any of the independent and/or dependent claims, Applicant respectfully requests, in the interests of compact prosecution, that the Office apply art against each feature of each rejected independent and dependent claims, on the record, and with specificity sufficient to support a prima facie case of obviousness.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

It is well known that in order for any prior-art references themselves to be validly combined for use in a prior-art § 103 rejection, *the references themselves* (or some other prior art) must suggest that they be combined. E.g., as was stated in *In re Sernaker*, 217 U.S.P.Q. 1, 6 (C.A.F.C. 1983):

“[P]rior art references in combination do not make an invention obvious unless something in the prior art references would suggest the advantages to be derived from combining their teachings.” That the suggestion to combine the references should not

come from applicant was forcefully stated in *Orthopedic Equipment Co. v. United States*, 217 U.S.P.Q. 193, 199 (C.A.F.C. 1983):

“It is wrong to use the patent in suit [here the patent application] as a guide through the maze of prior art references, combining the right references in the right way to achieve the result of the claims in suit [here the claims pending]. Monday morning quarterbacking is quite improper when resolving the question of nonobviousness in a court of law [here the PTO].” As was further stated in *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (C.A.F.C. 1988), “[w]here prior-art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself ... *Something in the prior art must suggest the desirability and thus the obviousness of making the combination.*” [Emphasis supplied.]

In line with these decisions, the Board stated in *Ex parte Levengood*, 28 U.S.P.Q.2d 1300 (P.T.O.B.A.&I. 1993):

“In order to establish a *prima facie* case of obviousness, it is necessary for the examiner to present *evidence*, preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, or in the form of generally available knowledge, that one having ordinary skill in the art *would have been led* to combine the relevant teachings of the, applied references in the proposed manner to arrive at the claimed invention. ...

That which is within the capabilities of one skilled in the art is not synonymous with obviousness. ... That one can *reconstruct* and/or explain the theoretical mechanism of an invention by means of logic and sound scientific reasoning does not afford the basis for an obviousness conclusion unless that logic and reasoning also supplies sufficient impetus to have led one of the ordinary skill in the art to combine the teachings of the references to make the claimed invention.... Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden

of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that 'would lead' that individual 'to combine the relevant teachings of the references.' ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done."

In the present case, there is no reason given in the last Office action to support the proposed combination. However the fact that the cited references have a general teaching, not specifically related to the claimed invention in this patent application, on DNA construct with insulin sequence and signal peptide region is not sufficient to gratuitously and selectively suggest that the one would be led to substitute parts of one reference for a part of another reference in order to meet applicants' novel claimed combination.

The references relied upon fail to provide an adequate basis in evidence to support the Examiner's initial conclusion of obviousness. In short there must be more than merely establishing that the individual components exist in the prior art. There must be something, found in the prior art which would have suggested, led or motivated one skilled in this art to bring those individual components together in the manner presently claimed. The present rejection lacks this aspect.

Applicants respectfully request, if the claims are again rejected upon any combination of references, that the Examiner include an explanation, in accordance with M.P.E.P. § 706.02. Ex parte Clapp, 27 U.S.P.Q. 972 (P.O.B.A. 1985), and Ex parte Levengood, supra, a "factual basis to support his conclusion that would have been obvious" to make the combination.

The Examiner has not persuasively explained why a person of ordinary skill in the art would have had a reason to modify the compositions

taught by Markussen, Schweden, Hollenberg, or Weidemann in a way that would result in the compositions defined by the claims in this patent application. Therefore, the Examiner has not made out a prima facie case of obviousness under 35 U.S.C. § 103. It is respectfully requested that this rejection be reconsidered and withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance and notification to that effect is earnestly requested. If desired, the examiner is invited to conduct a telephone conference to expedite the prosecution of the subject application. In such a case, the examiner is invited to call the undersigned attorney.

Should any official at the United States Patent and Trademark Office deem that any further action by the Applicants or Applicants' undersigned representative is desirable and/or necessary, the official is invited to telephone the undersigned at the number set forth below.

The Commissioner is hereby authorized to charge any fees which may be required regarding this application under 37 CFR §§ 1.16-1.17 or credit any overpayment, to deposit account No. 503321. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, or otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 503321.

Respectfully submitted,

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